(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 November 2001 (08.11.2001)

PCT

(10) International Publication Number
WO 01/83457 A2

(51) International Patent Classification[7]: C07D 235/32, A61K 31/4184, A61P 35/00

(21) International Application Number: PCT/US01/13543

(22) International Filing Date: 26 April 2001 (26.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/791,986 28 April 2000 (28.04.2000) US
09/562,709 28 April 2000 (28.04.2000) US

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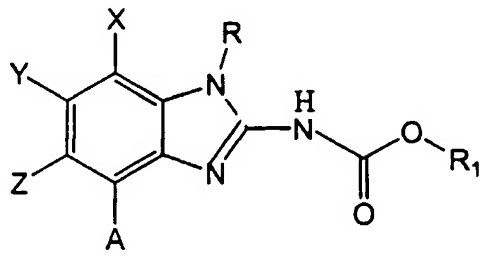
(81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CANCER TREATMENT



(I)

(57) Abstract: This invention is a method of treating cancer, including carcinomas and sarcomas through the administration of a pharmaceutical composition containing a tetra-substituted benzimidazole carbamate. The tetra-substituted benzimidazole carbamate is selected from the group consisting of formula (I), wherein X, Y, Z and A are independently selected from the group consisting of bromo, fluoro, chloro, iodo and alkyl of less than 4 carbon atoms or alkoxy of less than 4 carbon atoms; and R is hydrogen, alkylaminocarbonyl wherein the alkyl group has from 1 to 4 carbon atoms or an alkyl group of from 1 to 8 carbon atoms and R_1 is aliphatic hydrocarbon of less than 7 carbon atoms; or its pharmaceutically acceptable salts; or prodrugs thereof. Preferably R_1 is an alkyl group of less than 3 carbon atoms and X, Y, Z and A are halogen. Most preferred is 2-methoxycarbonylamino-4,5,6,7-tetrafluorobenzimidazole. The tetra-substituted benzimidazole carbamate and pharmaceutical compositions containing them are claimed herein. X, Y, Z and A are preferably electron withdrawing groups.

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CANCER TREATMENT

The present application is a continuation-in-part of U.S. Serial No. 09/791,986, filed April 28, 2000 and U.S. Serial No. 09/562,709, filed April 28, 2000. The patent applications are incorporated by reference herein.

TECHNICAL FIELD

This invention relates to a method of treating cancer, including carcinomas and sarcomas, with a tetra-substituted benzimidazole carbamate. Tetra-substituted benzimidazole carbamate compounds and the pharmaceutical composition containing tetra-substituted benzimidazole carbamate are also disclosed.

BACKGROUND OF THE INVENTION

Cancers are a leading cause of death in animals and humans. The exact cause of cancer is not known, but links between certain activities such as smoking or exposure to carcinogens and the incidence of certain types of cancers and tumors has been shown by a number of researchers.

Many types of chemotherapeutic agents have been shown to be effective against cancers and tumor cells, but not all types of cancers and tumors respond to these agents. Unfortunately, many of these agents also destroy normal cells. The exact mechanism for the action of these chemotherapeutic agents is not always known.

Despite advances in the field of cancer treatment the leading therapies to date are surgery, radiation and chemotherapy. Chemotherapeutic approaches are said to fight cancers that are metastasized or ones that are particularly aggressive. Such cytocidal or cytostatic agents work best on cancers with large growth factors, i.e., ones whose cells are rapidly dividing. To date, hormones, in particular estrogen, progesterone and testosterone, and some antibiotics produced by a variety of microbes, alkylating agents, and anti-metabolites form the bulk of therapies available to oncologists. Ideally cytotoxic agents that have specificity for cancer and tumor cells while not affecting normal cells would be extremely desirable. Unfortunately, none have been found and instead agents which target especially rapidly dividing cells (both tumor and normal) have been used.

The development of materials that would target tumor cells due to some unique specificity for them would be a breakthrough. Alternatively, materials that were cytotoxic to tumor cells while exerting mild effects on normal cells are also desirable.

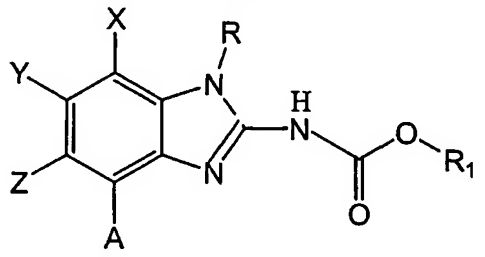
Carbendazim or 2-methoxycarbonylaminobenzimidazole has been studied as a cancer treatment. See US 5,767,138 issued June 16, 1998 to J. B. Camden. Carbendazim metabolizes in

the body through the hydroxylation of the benzene ring, primarily in the 5 position. The metabolite is not as active in the treatment of cancer as 2-methoxycarbonylaminobenzimidazole. Therefore, a benzimidazole carbamate compound that does not metabolize by this pathway would be a preferred material for cancer treatment.

It has been found that tetra-substituted benzimidazole carbamates, and in particular, those which are substituted with electron withdrawing groups, can be used to treat cancer.

SUMMARY OF THE INVENTION

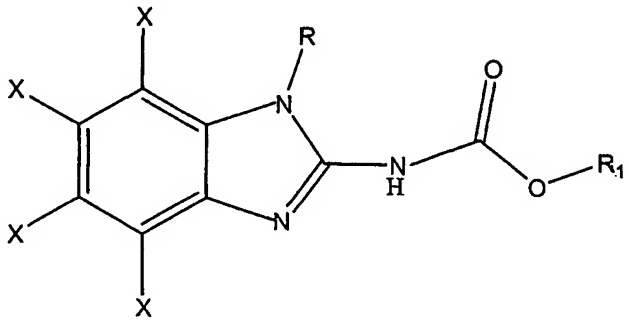
The tetrasubstituted benzimidazole carbamates have the formula:



wherein X, Y, Z and A are independently selected from the group consisting of electron withdrawing groups, preferably from the group consisting of bromo, fluoro, chloro, iodo and alkyl of less than 4 carbon atoms or alkoxy of less than 4 carbon atoms; and R is hydrogen, alkylaminocarbonyl or an alkyl group of from 1 to 8 carbon atoms and R_1 is alkyl of less than 7 carbon atoms. Preferably R_1 is an alkyl group of less than 4 carbon atoms. The preferred compound is a benzimidazole carbamate wherein A, X, Y and Z are fluorine. Other preferred compounds are the dimethyldifluoro analogs, tetrachloro analogs and trifluoromethyl analogs. The salts and prodrugs of the benzimidazole carbamate are also useful herein.

The preferred salts are inorganic salts.

Preferably the compound has the formula:



wherein X is fluoro, chloro, bromo, iodo or methyl and R is methyl or hydrogen and R_1 is methyl or ethyl.

Claimed herein is a method of treating cancer, in particular, treating cancers in warm blooded animals and humans, comprising administering a therapeutically effective amount of a composition comprising one or more tetra-substituted benzimidazole carbamate compounds, a salt or prodrug thereof.

The present invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a tetra-substituted benzimidazole carbamate, including the pharmaceutical acceptable salts or its prodrugs.

These compositions have been discovered to inhibit the growth of cancer or other tumors in humans or animals by administration of a therapeutically effective amount of the composition, preferably by administering tetra-substituted benzimidazole carbamate to the site of the cancer.

More specifically, this invention provides an anti-cancer composition comprising a pharmaceutical carrier and tetra-substituted benzimidazole carbamate as defined herein along with a method for treating such cancers. The composition can be used in conjunction with other chemotherapeutic agents and other cancer treatments.

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions:

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

As used herein, the term "safe and effective amount" refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. By "therapeutically effective amount" is meant an amount of a compound of the present invention effective to yield the desired therapeutic response. For example, an amount effective to delay the growth of or to cause a cancer, either a sarcoma or lymphoma, or to shrink the cancer or prevent metastasis. The specific safe and effective amount or therapeutically effective amount will vary with such factors as the particular condition being treated, the physical condition of the patient, the type of mammal or animal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compounds or its derivatives.

As used herein, a "pharmaceutical salt" is salt of the tetra-substituted benzimidazole carbamate which has been modified by making acid or base salts of the compounds. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines. Preferably the salts are made using an organic or inorganic acid.

These preferred acid salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like. The most preferred salt is the hydrochloride salt.

As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle, for delivering the tetra-substituted benzimidazole carbamate to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind. Liposomes are also a pharmaceutical carrier.

As used herein, "cancer" refers to all types of cancer or neoplasm or malignant tumors found in mammals, including carcinomas and sarcomas. Examples of cancers are cancer of the breast, pancreas, colon, lung, non-small cell lung, ovary, and prostate.

The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease- acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood- leukemic or aleukemic (subleukemic). The P388 leukemia model is widely accepted as being predictive of in vivo anti-leukemic activity. It is believed that compound that tests positive in the P388 assay will generally exhibit some level of anti-leukemic activity in vivo regardless of the type of leukemia being treated. Accordingly, the present invention includes a method of treating leukemia, and, preferably, a method of treating acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, and undifferentiated cell leukemia.

The term "sarcoma" generally refers to a tumor which is made up of a substance like the

embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas which can be treated with tetra-substituted benzimidazole carbamate and optionally a potentiator and/or chemotherapeutic agent include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abernethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Éwing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Ŕous sarcoma, serocystic sarcoma, synovial sarcoma, and telangiectaltic sarcoma.

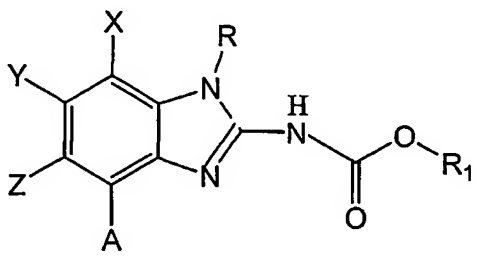
The term "melanoma" generally refers to a tumor arising from the melanocytic system of the skin and other organs. Melanomas which can be treated with tetra-substituted benzimidazole carbamate and optionally a potentiator and/or another chemotherapeutic agent include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, and superficial spreading melanoma.

The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas which can be treated with tetra-substituted benzimidazole carbamate and optionally a potentiator and/or a chemotherapeutic agent include, for example, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniform carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-

matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hürthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, and carcinoma villosum.

Additional cancers which can be treated with tetra-substituted benzimidazole carbamate according to the invention include, for example, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, breast cancer, ovarian cancer, lung cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, small-cell lung tumors, primary brain tumors, stomach cancer, colon cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, cervical cancer, endometrial cancer, adrenal cortical cancer, and prostate cancer.

As used herein, "tetra-substituted benzimidazole carbamate " or "tetra-substituted benzimidazole carbamate compound" are used interchangeably to mean those chemicals having the formula:



wherein X, Y, Z and A are independently selected from the group consisting of bromo, fluoro, chloro, iodo and alkyl of less than 4 carbon atoms or alkoxy of less than 4 carbon atoms; and

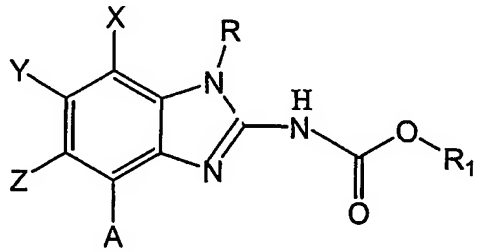
R is hydrogen, alkylaminocarbonyl wherein the alkyl group has from 1 to 4 carbon atoms or an alkyl group of from 1 to 8 carbon atoms and R_1 is aliphatic hydrocarbon of less than 7 carbon atoms and pharmaceutically acceptable salts or prodrugs thereof. Preferably R_1 is an alkyl group of less than 3 carbon atoms and R is hydrogen or (butylamino)carbonyl. More specific tetra-substituted benzimidazole carbamates are described in detail below.

By "alkyl" as used herein is meant a straight, branched or cyclic alkane derivatives. Preferably the alkyl is methyl or ethyl. While tert-butyl is a preferred alkyl, it is generally not present as more than one substituent due to its size.

As used herein "combination therapy" or "adjunct therapy" means that the patient in need of the drug is treated or given another drug for the disease in conjunction with the tetra-substituted benzimidazole carbamate. This combination therapy can be sequential therapy where the patient is treated first with one drug and then the other or two or more drugs are given simultaneously.

B. THE TETRA-SUBSTITUTED BENZIMIDAZOLE CARBAMATE

The compounds have the following structure:



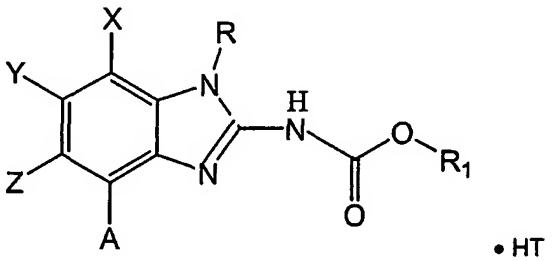
wherein X, Y, Z and A are independently selected from the group consisting of bromo, fluoro, chloro, iodo and alkyl of less than 4 carbon atoms or alkoxy of less than 4 carbon atoms; and R is hydrogen, alkylaminocarbonyl wherein the alkyl group has from 1 to 4 carbon atoms or an alkyl group of from 1 to 8 carbon atoms and R_1 is aliphatic hydrocarbon of less than 7 carbon atoms and its pharmaceutically acceptable salts and prodrugs thereof. Preferably R_1 is an alkyl group of less than 3 carbon atoms and R is hydrogen or (butylamino)carbonyl.

Some useful compounds include: 2-methoxycarbonylamino-4,5,6,7-tetrafluorobenzimidazole, 1-(butylamino)carbonyl 2-methoxycarbonylamino-4,5,6,7-tetrafluorobenzimidazole, 1-(butylamino)carbonyl 2-methoxycarbonylamino-4,5,6,7-tetrafluorobenzimidazole hydrochloride, 2-methoxycarbonylamino-4,5,6,7-tetrafluorobenzimidazole hydrochloride, 2-methoxycarbonylamino-4,5,6,7-tetrachlorobenzimidazole, 2- methoxycarbonylamino-4,5,6,7-

tetrabromobenzimidazole, 2-methoxycarbonylamino-4,5,6,7- tetraiodobenzimidazole, 2-methoxycarbonylamino-4,5-difluoro-6,7-dimethylbenzimidazole, 2-methoxycarbonylamino-4,5,6- trifluoro-7-methylbenzimidazole, 2-methoxycarbonylamino-4,5,6-trifluoro-7-methylbenzimidazole, 2-methoxycarbonylamino-4,5-dichloro-6,7-difluorobenzimidazole, and analogs thereof.

Salts

Tetra-substituted benzimidazole carbamate salt has the formula:



wherein X, Y, Z and A are independently selected from the group of bromo, fluoro, chloro, iodo and alkyl of less than 4 carbon atoms or alkoxy of less than 4 carbon atoms; and R is hydrogen or an alkyl group of from 1 to 8 carbon atoms and R_1 is alkyl of less than 7 carbon atoms and HT is an inorganic or organic acid.

As above, X,Y,Z and A can be the same or can be varied. If R is hydrogen, then it is possible to have more than one acid salt.

The salts of the tetra-substituted benzimidazole carbamate include the conventional non-toxic salts or the quaternary ammonium salts of the tetra-substituted benzimidazole carbamate formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, formic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The preferred salt is the hydrochloride salt.

The salts of the present invention are synthesized from the tetra-substituted benzimidazole carbamate which contains a basic moiety by conventional chemical methods. Generally, such salts are prepared by reacting the free base forms of these compounds with a stoichiometric amount of the appropriate acid in water or in an organic solvent, or in a mixture of the two; generally,

nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418.

Prodrugs

The tetra-substituted benzimidazole carbamate compounds also include prodrugs. "Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug according to the formula of the tetra-substituted benzimidazole carbamate described above in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the tetra-substituted benzimidazole carbamate compound are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds wherein amine groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free amino group. Examples of prodrugs include, but are not limited to, acetate, formate, or benzoate derivatives of amine functional groups in the tetra-substituted benzimidazole carbamates; and the like.

Synthesis

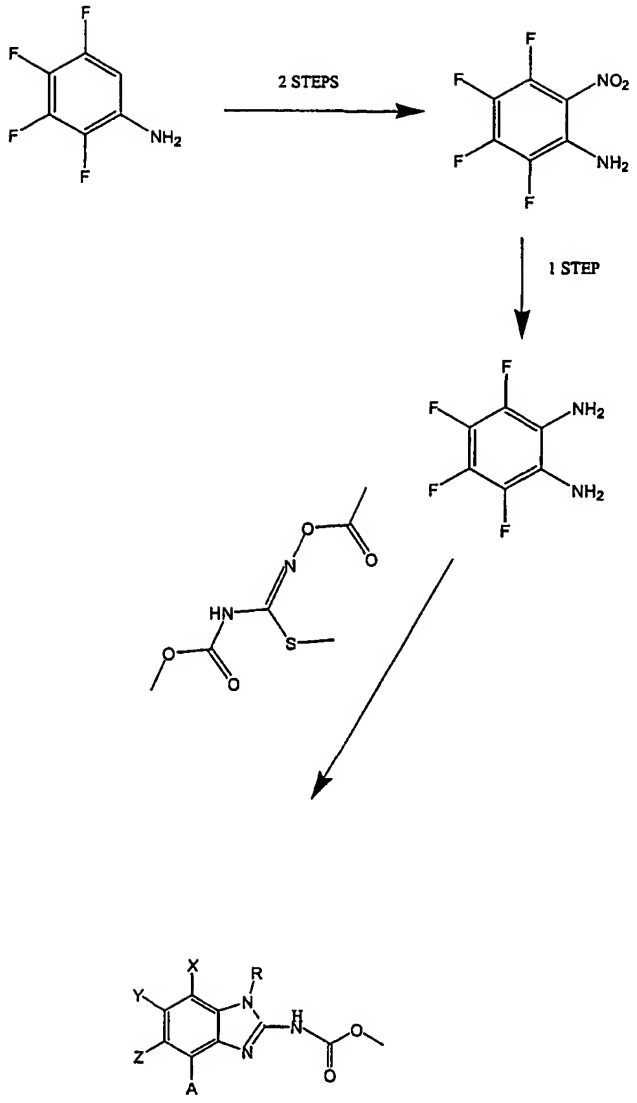
The tetra-substituted benzimidazole carbamate is prepared in a number of ways well known to one skilled in the art of organic synthesis. They can be synthesized by starting with a tetra-substituted aminobenzene, for example, 2,3,4,5-tetrafluoroaniline. The aminobenzene is nitrated under conditions that do not affect the substituents and then reduced to a 1,2-diaminotetrasubstituted benzene. The hydrogenation can be carried out using hydrogen in presence of palladium on carbon or by other standard techniques. This compound is then converted to the tetrasubstituted benzimidazole by cyclizing with isothiourea reagent. Isothiourea is prepared from 2-methyl-2-thiopseudourea sulfate and methyl chloroformate by reaction in a water-dichloromethane system under phase transfer conditions. Scheme 1 illustrates the synthesis of the tetrafluoro material.

An alternative synthesis for tetrafluorobenzimidazole carbamate starts with 1-nitro-2,3,4,5,6 pentafluorobenzene. The 1-nitro-2,3,4,5,6 pentafluorobenzene is converted to 1-nitro-2-amino-3,4,5,6-tetrafluorobenzene. (See A. Heaton, et al., Journal of Fluorine Chemistry, 81 (1997), 133-138 and G. M. Brooks, et al., J. Chem. Soc., 1961, 802-807.) The 1-nitro-2-amino-3,4,5,6-tetrafluorobenzene can then be reduced to the 1,2-diamino-3,4,5,6 tetrafluorobenzene and converted to the benzimidazole by cyclizing with the isothiourea reagent as above. This method is illustrated in scheme 2.

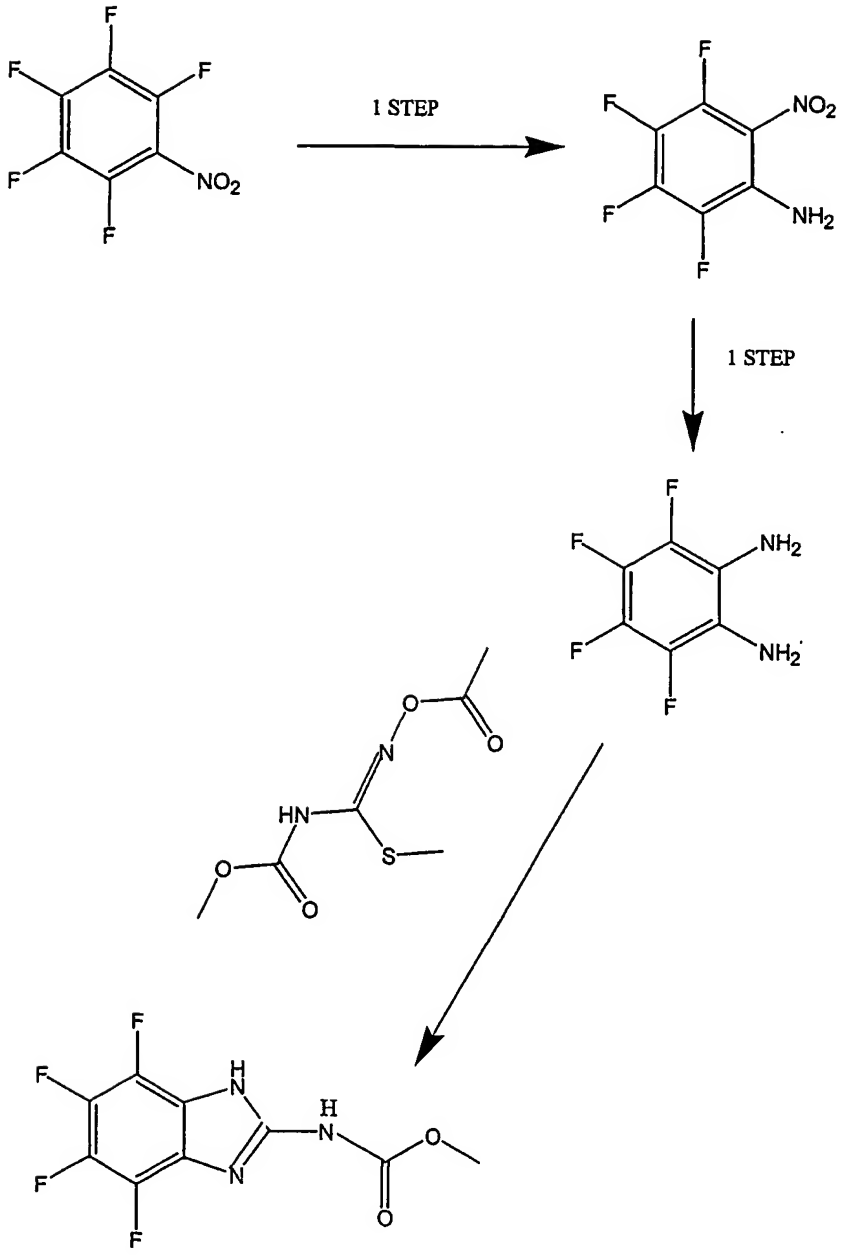
One skilled in the art of organic synthesis can modify these reaction to make other

compounds useful herein.

Scheme 1



Scheme 2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C. Combination Therapy

In some embodiments, tetra-substituted benzimidazole carbamate is used in combination with one or more potentiators and/or chemotherapeutic agents for the treatment of cancer or tumors. These combinations can be administered together or sequentially.

An exemplary potentiator is triprolidine or its cis-isomer which are used in combination with chemotherapeutic agents and tetra-substituted benzimidazole carbamates. Triprolidine is described in US 5,114,951 (1992). Another potentiator is procodazole, 1H-Benzimidazole carbamate-2-propanoic acid; [ß-(2-benzimidazole carbamate) propionic acid; 2-(2-carboxyethyl)benzimidazole carbamate; propazol]. Procodazole is a non-specific immunoprotective agent active against viral and bacterial infections. It is effective with tetra-substituted benzimidazole carbamate in treating cancers, tumors or leukemia. Procodazole can also be combined with tetra-substituted benzimidazole carbamate and other chemotherapeutic agents to treat cancer, tumor or leukemia.

Other potentiators which can be used with tetra-substituted benzimidazole carbamate and optionally another chemotherapeutic agent to treat or inhibit the growth of cancer include monensin, an anti-sense inhibitor of the RAD51 gene, bromodeoxyuridine, dipyridamole, indomethacin, a monoclonal antibody, an anti-transferrin receptor immunotoxin, metoclopramide, 7-thia-8-oxoguanosine, N-solanesyl-N,N'-bis(3,4-dimethoxybenzyl) -ethylenediamine, leucovorin, heparin, N-[4-[(4-fluorphenyl)sulfonly]phenyl] acetamide, heparin sulfate, cimetidine, a radiosensitizer, a chemosensitizer, a hypoxic cell cytotoxic agent, muramyl dipeptide, vitamin A, 2'-deoxycoformycin, a bis-diketopiperazine derivative, and dimethyl sulfoxide.

The chemotherapeutic agents which can be used with tetra-substituted benzimidazole carbamate and an optional potentiator are generally grouped as DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents and others such as Asparaginase or hydroxyurea. Each of the groups of chemotherapeutic agents can be further divided by type of activity or compound. The chemotherapeutic agents used in combination with tetra-substituted benzimidazole carbamate include members of all of these groups. For a detailed discussion of chemotherapeutic agents and their method of administration, see Dorr, et al, *Cancer Chemotherapy Handbook,* 2d edition, pages 15-34, Appleton & Lange (Connecticut, 1994).

DNA-Interactive Agents include the alkylating agents, e.g. Cisplatin, Cyclophosphamide, Altretamine; the DNA strand-breakage agents, such as Bleomycin; the intercalating topoisomerase II inhibitors, e.g., Dactinomycin and Doxorubicin); the nonintercalating topoisomerase II inhibitors such as, Etoposide and Teniposde; and the DNA minor groove binder Plicamydin.

The alkylating agents form covalent chemical adducts with cellular DNA, RNA, and protein molecules and with smaller amino acids, glutathione and similar chemicals. Generally, these alkylating agents react with a nucleophilic atom in a cellular constituent, such as an amino, carboxyl, phosphate, sulfhydryl group in nucleic acids, proteins, amino acids, or glutathione. The mechanism and the role of these alkylating agents in cancer therapy is not well understood. Typical alkylating agents include:

Nitrogen mustards, such as Chlorambucil, Cyclophosphamide, Isofamide, Mechlorethamine, Melphalan, Uracil mustard;

Aziridine such as Thiotepa;

methanesulphonate esters such as Busulfan;

nitroso ureas, such as Carmustine, Lomustine, Streptozocin;

platinum complexes, such as Cisplatin, Carboplatin;

bioreductive alkylator, such as Mitomycin, and Procarbazine, Dacarbazine and Altretamine.

DNA strand breaking agents include Bleomycin.

DNA topoisomerase II inhibitors include the following:

Intercalators, such as Amsacrine, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, and Mitoxantrone; and

nonintercalators, such as Etoposide and Teniposide.

The DNA minor groove binder is Plicamycin.

The antimetabolites interfere with the production of nucleic acids by one or the other of two major mechanisms. Some of the drugs inhibit production of the deoxyribonucleoside triphosphates that are the immediate precursors for DNA synthesis, thus inhibiting DNA replication. Some of the compounds are sufficiently like purines or pyrimidines to be able to substitute for them in the anabolic nucleotide pathways. These analogs can then be substituted into the DNA and RNA instead of their normal counterparts. The antimetabolites useful herein include:

folate antagonists such as Methotrexate and trimetrexate

pyrimidine antagonists, such as Fluorouracil, Fluorodeoxyuridine, CB3717, Azacitidine and Floxuridine

purine antagonists such as Mercaptopurine, 6-Thioguanine, Pentostatin;

sugar modified analogs such as Cytarabine and Fludarabine; and

ribonucleotide reductase inhibitors such as hydroxyurea.

Tubulin Interactive agents act by binding to specific sites on tubulin, a protein that

polymerizes to form cellular microtubules. Microtubules are critical cell structure units. When the interactive agents bind on the protein, the cell cannot form microtubules. Tubulin Interactive agents include colchicine, Vincristine and Vinblastine, both alkaloids and Paclitaxel and cytoxan.

Hormonal agents are also useful in the treatment of cancers and tumors. They are used in hormonally susceptible tumors and are usually derived from natural sources. These include:

estrogens, conjugated estrogens and Ethinyl Estradiol and Diethylstilbesterol, Chlortrianisen and Idenestrol;

progestins such as Hydroxyprogesterone caproate, Medroxyprogesterone, and Megestrol; and

androgens such as testosterone, testosterone propionate; fluoxymesterone, methyltestosterone.

Adrenal corticosteroids are derived from natural adrenal cortisol or hydrocortisone. They are used because of their anti inflammatory benefits as well as the ability of some to inhibit mitotic divisions and to halt DNA synthesis. These compounds include, Prednisone, Dexamethasone, Methylprednisolone, and Prednisolone.

Leutinizing hormone releasing hormone agents or gonadotropin-releasing hormone antagonists are used primarily the treatment of prostate cancer. These include leuprolide acetate and goserelin acetate. They prevent the biosynthesis of steroids in the testes.

Antihormonal antigens include:

antiestrogenic agents such as Tamoxifen,

antiandrogen agents such as Flutamide; and

antiadrenal agents such as Mitotane and Aminoglutethimide.

Hydroxyurea, which appears to act primarily through inhibition of the enzyme ribonucleotide reductase, can also be used in combination with tetra-substituted benzimidazole carbamates.

Asparaginase is an enzyme which converts asparagine to nonfunctional aspartic acid and thus blocks protein synthesis in the tumor. Asparaginase can also be used in combination with tetra-substituted benzimidazole carbamate to treat cancer.

D. Dosage

Tetra-substituted benzimidazole carbamate is preferably micronized or powdered so that it is more easily dispersed and solubilized or absorbed by the body. Processes for grinding or pulverizing drugs are well known in the art. For example, a hammer mill or similar milling device are used. The preferred particle size is less than about 100μ and preferably less than 50μ.

Dosage forms (compositions) suitable for internal administration contain from about 1.0 milligram to about 5000 milligrams of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. Based on the body weight of the patient, the dosage may be administered in one or more doses several times per day or per week. Multiple dosage units may be required to achieve a therapeutically effective amount. For example, if the dosage form is 1000 mg, and the patient weighs 40 kg, one pill will provide a dose of 25 mg per kg for that patient. It will provide a dose of only 12.5 mg/kg for a 80 kg patient.

Tetra-substituted benzimidazole carbamate has exhibited efficacy *in vivo* against cancers in mice at doses of about 1000 mg/kg, 2000 mg/kg and 4000 mg/kg. Generally, an effective dose in mice is about 12 times the expected effective dose in humans. By way of general guidance, for humans a dosage of as little as about 25 milligrams (mg) per kilogram (kg) of body weight and up to about 10,000 mg per kg of body weight is suitable as a therapeutically effective dose. Preferably, from about 40 mg/kg to about 2500 mg/kg of body weight is used. Other preferred doses range between 100 mg/kg to about 3000 mg/kg of body weight. However, a dosage of between about 2 milligrams (mg) per kilogram (kg) of body weight to about 400 mg per kg of body weight is also suitable for treating some cancers.

Intravenously, the most preferred rates of administration may range from about 1 to about 1000 mg/kg/minute during a constant rate infusion. Tetra-substituted benzimidazole carbamate can be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily. Tetra-substituted benzimidazole carbamate is generally given in one or more doses on a daily basis or from one to three times a week.

Tetra-substituted benzimidazole carbamate is administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in combination with other therapeutic agents

The amount and identity of a chemotherapeutic agent that is used with tetra-substituted benzimidazole carbamate in treating cancer, tumor, leukemia, or other related diseases will vary according to patient response and physiology, type and severity of side effects, disease being treated, dosing regimen, patient prognosis or other such factors.

When tetra-substituted benzimidazole carbamate is used in combination with other therapeutic agents, the ratio of tetra-substituted benzimidazole carbamate to the other therapeutic agent will be varied as needed according to the desired therapeutic effect, the observed side effects of the combination, or other such considerations known to those of ordinary skill in the medical arts. Generally, the ratio of tetra-substituted benzimidazole carbamate to other

therapeutic agent will range from about 0.5% : 99.5% to about 99.5% : 0.5% on a weight basis.

When tetra-substituted benzimidazole carbamate is administered before or after other therapeutic agents to treat cancer, tumors, or other diseases, the respective doses and the dosing regimen of tetra-substituted benzimidazole carbamate and the other therapeutic agent may vary. The adjunct or combination therapy can be sequential, that is the treatment with one agent first and then the second agent, or it can be concomitant treatment wherein two or more agents are administered substantially at the same time. The sequential therapy can be within a reasonable time after the completion of the first therapy before beginning the second therapy. The treatment with both agents at the same time can be in the same daily dose or in separate doses. For example treatment with one agent on day 1 and the other on day 2. The exact regimen will depend on the disease being treated, the severity of the disease and the response to the treatment.

For example, a full dosing regimen of tetra-substituted benzimidazole carbamate can be administered either before or after a full dosing regimen of the other therapeutic agent, or alternating doses of tetra-substituted benzimidazole carbamate and the other therapeutic agent may be administered. As a further example, tetra-substituted benzimidazole carbamate can be administered concomitantly with the other therapeutic agent.

The identity of the chemotherapeutic agent, the pharmaceutical carrier and the amount of compound administered will vary widely depending on the species and body weight of mammal and the type of cancer being treated. The dosage administered will vary depending upon known factors, such as the pharmacodynamic characteristics of a specific chemotherapeutic agent and its mode and route of administration; the age, sex, metabolic rate, absorptive efficiency, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment being administered; frequency of treatment; and desired therapeutic effect.

Tetra-substituted benzimidazole carbamates, the potentiator and/or the chemotherapeutic agent are administered together in a single dosage form or separately in two or more different dosage forms. These can be administered independently by the same route or by two or more different routes of administration depending on the dosage forms employed.

Suitable pharmaceutical compositions and dosage forms will preferably comprise tetra-substituted benzimidazole carbamates, a potentiator and optionally a chemotherapeutic agent. The ratio of tetra-substituted benzimidazole carbamate to potentiator is generally in the range of about 1:0.01 to 10:1, and preferably 1:0.05 to 1:1 on a weight basis.

One skilled in the art will be able to ascertain the appropriate dose.

E. Dosage Form

A dosage unit may comprise a single compound or mixtures thereof with other anti-

cancer compounds, other cancer or tumor growth inhibiting compounds. Tetra-substituted benzimidazole carbamate can be administered in oral dosage forms as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Tetra-substituted benzimidazole carbamate may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

Tetra-substituted benzimidazole carbamate is typically administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or carriers (collectively referred to herein as a pharmaceutically acceptable carrier or carrier materials) suitably selected with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The unit will be in a form suitable for oral, rectal, topical, intravenous injection or parenteral administration.

Tetra-substituted benzimidazole carbamate can be administered alone but is generally mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid, and the type of carrier is generally chosen based on the type of administration being used.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U. S. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7. (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers : Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.).

Tablets may contain suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with

an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like.

Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Tetra-substituted benzimidazole carbamate can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Tetra-substituted benzimidazole carbamate may also be coupled to soluble polymers as targetable drug carriers or as a prodrug. Such polymers include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide-phenol, polyhydroxyethylasparta-midephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, tetra-substituted benzimidazole carbamate may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as immediate release products or as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

For oral administration in liquid dosage form, the oral drug components are combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from

non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Tetra-substituted benzimidazole carbamate may also be administered in intranasal form via use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will generally be continuous rather than intermittant throughout the dosage regimen.

Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Useful pharmaceutical dosage forms for administration of tetra-substituted benzimidazole carbamates are illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 10 to 500 milligrams of powdered active ingredient, 5 to 150 milligrams of lactose, 5 to 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 - 500 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit

was 100 - 500 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 50-275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable solution

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 ml contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 ml of vanillin.

Kits

The present invention also includes pharmaceutical kits useful, for example, for the treatment of cancer, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of tetra-substituted benzimidazole carbamates. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Printed instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit. It should be understood that although the specified materials and conditions are important in practicing the invention, unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

The chemotherapeutic agents, tetra-substituted benzimidazole carbamate and, optionally, the potentiators are typically mixed with a pharmaceutically acceptable carrier as described above.

Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

F. Method of Treatment

The method of treatment can be any suitable method which is effective in the treatment of the particular cancer or tumor type being treated. Treatment may be oral, rectal, topical, parenteral or intravenous administration or by injection into the tumor or cancer. The method of

administering an effective amount also varies depending on the disorder or disease being treated. It is believed that parenteral treatment by intravenous, subcutaneous, or intramuscular application of the tetra-substituted benzimidazole carbamates, formulated with an appropriate carrier, additional cancer inhibiting compound or compounds or diluent to facilitate application will be the preferred method of administering the compounds to warm blooded animals.

One skilled in the art will recognize that the efficacy of the tetra-substituted benzimidazole carbamates can be ascertained through routine screening using known cancer cell lines both in vitro and in vivo. Cell lines are available from American Tissue Type Culture or other laboratories.

The following examples are illustrative and not intended to be limiting of the invention.

Example 1

2-Methoxycarbonylamino-4,5,6,7- tetrafluorobenzimidazole (tetrafluoro) was used to treat SK-OV-3 tumor lines in nude mouse. The average tumor weight is reported in mg. The control was the vehicle given twice a week and also 5 times a week. The 2-methoxycarbonyl-amino-4,5,6,7- tetrafluorobenzimidazole was also given on this same schedule. Both compounds were administered by oral gavage. There is a dose responsive effect on the growth of the tumor in the mice treated with the 2-Methoxycarbonylamino-4,5,6,7- tetrafluorobenzimidazole.

Compound	Average Tumor Weight				
	day 1	day 5	day 9	day 12	day 15
Control 2x wkly	59.9	151.2	364.5	687.8	1070.5
Control qdx5	59.9	117.2	237.6	498.6	852.2
Tetrafluoro- 2000 mg/kg 2x wkly	58.5	108.1	246.8	476.2	770
Tetrafluoro- 4000 mg/kg 2x wkly	59.5	98.6	204	336.6	672.9
Tetrafluoro- 2000 mg/kg qdx5	59.1	106.2	255.8	381.7	781.2
Tetrafluoro-4000 mg/kg qdx5	59.5	66.1	150.8	160.7	315.8

Example 2

Preparation of 1-nitro-2 amino-3,4,5,6-tetrafluorobenzene

Dry ammonia gas was passed through a solution of pentafluoronitrobenzene (100 gm,

0.47 mol) in diethyl ether (3 liter), at room temperature for 3 hours with stirring. Stirring was continued for an additional 18 hours. The mixture was then filtered to removed the precipitated ammonium fluoride. The filtrate (ether solution) was then washed with water, and then with brine (200 ml.), dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure and left a red solid. The solid was purified by flash column chromatography (silica gel; toluene/hexane 1:1) give 57.06 gm of the desired product as an orange solid.

Preparation of 2-methoxycarbonylamino-4,5,6,7-tetrafluorobenzimidazole

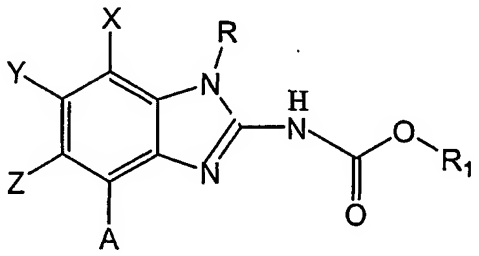
A solution of 2,3,4,5-tetrafluoro-6-nitroaniline (36.7 g, 0.17 mol) in ethanol (240 ml) containing 10% palladium on carbon (11.5 gm) in a 500 ml Parr bottle was hydrogenated in the Parr apparatus. When the yellow color of the solution has disappeared, the solution was filtered to remove the palladium on carbon. The solid was washed with ethanol. The combined filtrate was used for the next reaction without product isolation.

Ethanol was added to the filtrate to maintain a total volume of 600 ml. The solution was added to a two liter flask containing 600 ml of water and 11.1 ml of acetic acid, and N,N'-bismethoxycarbonyl-S-methylisothiourea (36 g, 0.17 mol). The mixture was heated at the reflux temperature for 3 hours. A solid precipitate formed.

The mixture was cooled to room temperature and filtered. The solid collected was washed with water and then with ethanol/water (1:1) to give a white fluffy solid.

What is claimed is:

1. A pharmaceutical composition comprising a therapeutically effective amount of a composition comprising a tetra-substituted benzimidazole carbamate having the formula:



wherein X, Y, Z and A are independently selected from the group consisting of bromo, fluoro, chloro, iodo and alkyl of less than 4 carbon atoms or alkoxy of less than 4 carbon atoms; and R is hydrogen, alkylaminocarbonyl wherein the alkyl group has from 1 to 4 carbon atoms or an alkyl group of from 1 to 8 carbon atoms and R_1 is aliphatic hydrocarbon of less than 7 carbon atoms or its pharmaceutically acceptable salts or prodrugs thereof.

2. A pharmaceutical composition of Claim 1 further comprising a pharmaceutical carrier.

3. A pharmaceutical composition according to Claims 1 or 2 comprising a safe and effective amount of a potentiator.

4. A pharmaceutical composition according to Claim 3, wherein said potentiator is selected from the group consisting of procodazole, triprolidine, propionic acid, monensin, an anti-sense inhibitor of the RAD51 gene, bromodeoxyuridine, dipyridamole, indomethacin, a monoclonal antibody, an anti-transferrin receptor immunotoxin, metoclopramide, 7-thia-8-oxoguanosine, N-solanesyl-N,N'-bis(3,4-dimethoxybenzyl)ethylenediamine, N-[4-[(4-fluorphenyl)sulfonly]phenyl] acetamide, leucovorin, heparin, heparin sulfate, cimetidine, a radiosensitizer, a chemosensitizer, a hypoxic cell cytotoxic agent, muramyl dipeptide, vitamin A, 2'-deoxycoformycin, a bis-diketopiperazine derivative, and dimethyl sulfoxide.

5. A pharmaceutical composition according to Claims 1,2, 3 or 4 further comprising a safe and effective amount of a chemotherapeutic agent.

6. A pharmaceutical composition according to Claim 5 wherein said chemotherapeutic agent

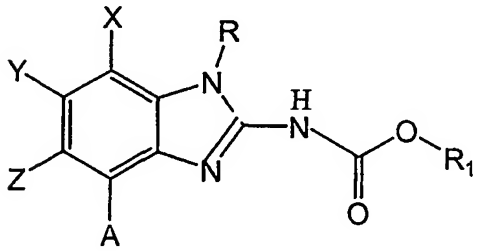
is selected from the group consisting of a DNA-interactive agent, alkylating agent, antimetabolite, tubulin-interactive agent, hormonal agent, Asparaginase and hydroxyurea.

7. A pharmaceutical composition according to Claim 5 wherein said chemotherapeutic agent is selected from the group consisting of Asparaginase, hydroxyurea, Cisplatin, Cyclophosphamide, Altretamine, Bleomycin, Dactinomycin, Doxorubicin, Etoposide, Teniposide, Paclitaxel, cytoxan, 2-methoxycarbonylaminobenzimidazole carbamate and Plicamycin.

8. A pharmaceutical composition according to Claim 7 wherein said chemotherapeutic agent is selected from the group consisting of Methotrexate, Fluorouracil, Fluorodeoxyuridine, CB3717, Azacitidine, Floxuridine, Mercaptopurine, 6-Thioguanine, Pentostatin, Cytarabine, and Fludarabine.

9. A pharmaceutical composition according to Claim 1,2,3,4,5,6,7 or 8 in the form of a liposome composition wherein said liposome is a unilamellar vesicle or multilamellar vesicle.

10. A tetra-substituted benzimidazole carbamate having the formula:



wherein X, Y, Z and A are independently selected from the group of electron withdrawing groups; and R is hydrogen, alkylaminocarbonyl wherein the alkyl group has from 1 to 4 carbon atoms, or an alkyl of from 1 to 8 carbon atoms and R_1 is alkyl of less than 7 carbon atoms.

11. A tetra-substituted benzimidazole carbamate according to Claim 10 or 11 wherein X, Y, Z and A are independently selected from the group consisting of bromo, fluoro, chloro, iodo and alkyl of less than 4 carbon atoms or alkoxy of less than 4 carbon atoms; R is hydrogen or (butylamino)carbonyl, and R_1 is an alkyl group of less than 4 carbon atoms.

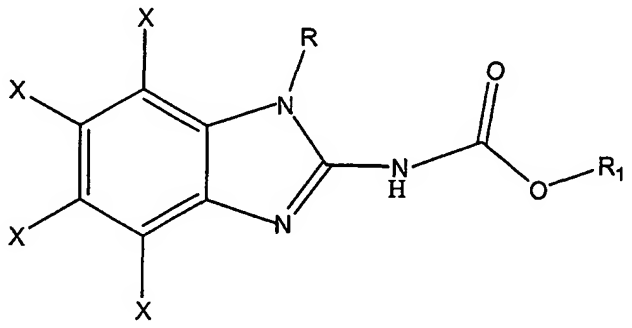
12. A tetra-substituted benzimidazole carbamate according to Claim 10 or 11 wherein X and Y are identical and Z and A are identical and wherein X, Y and Z , A are independently

selected from the group consisting of fluoro, chloro, bromo, iodo or methyl and R is (butylamino)carbonyl, methyl or hydrogen and R_1 is methyl or ethyl.

13. A tetra-substituted benzimidazole carbamate according to Claim 10 or 11 wherein X, Y and A are identical and wherein X, Y, A and Z are independently selected from the group consisting of fluoro, chloro, bromo, iodo or methyl and R is methyl, (butylamino)carbonyl, or hydrogen and R_1 is methyl or ethyl.

14. A tetra-substituted benzimidazole carbamate according to Claim 10 wherein A, Y and Z are identical and wherein X, Y, Z and A are independently selected from the group consisting of fluoro, chloro, bromo, iodo or methyl and R is methyl, (butylamino)carbonyl or hydrogen and R_1 is methyl or ethyl.

15. A tetra-substituted benzimidazole carbamate according to Claim 10 having the formula:



wherein X is fluoro, chloro, bromo, iodo or methyl and R is (butylamino)carbonyl, methyl or hydrogen and R_1 is methyl or ethyl.

16. A salt of a tetra-substituted benzimidazole carbamate of claims 10, 11, 12, 13, 14, or 15.

17. A salt of a tetra-substituted benzimidazole carbamate according to Claim 16 wherein the salt is made from an acid selected from the group consisting of hydrochlorides, hydrobromides, sulfate acids, nitrate acids, phosphate acids, acid sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates.

18. A prodrug of a tetra-substituted benzimidazole carbamate according to Claim 10,11,12,13,14,15,16 or 17.

19. Use of a pharmaceutical composition according to claims 1,2,3,4,5,6,7,8, or 9 to treat cancer.

20. A use according to Claim 19 wherein said cancer is selected from the group consisting of prostate cancer, melanoma, leukemia, pancreatic cancer, neuroblastoma, cervical cancer, ovarian cancer, stomach cancer, a sarcoma, a lymphoma, breast cancer, lung cancer and colon cancer.

21. A use according to claim 19 wherein the method of treating cancer comprises a combination therapy comprising a safe and effective amount of a chemotherapeutic agent along with the pharmaceutical composition.